REMARKS/ARGUMENTS

Claims 52 and 54-62 as submitted on November 19, 2010 are pending

No new issue for search or consideration

The following remarks and arguments are necessitated by the entry of the claims submitted on November 19, 2010 and further clarify the record in light of remarks in the Advisory Actions mailed December 2 and 22, 2010.

Applicants' remarks and arguments focus on art of record in the instant application, documents relied upon in the remaining asserted rejections, and specific issues of record. Therefore, there are no new issues for search or consideration.

Consideration of evidence under 37 C.F.R. § 1.116(e)

The remarks and arguments herein address facts underlying the cited Chapple et al. document ("Looking at protein misfolding neurodegenerative disease through retinitis pigmentosa" ANCR, 3(1):12-13, 2003). The evidence is in Reference 14 cited in Chapple et al.[1]

The evidence is needed for a proper understanding of Chapple et al. and is needed because the claims encompass administration of 9-*cis*-10-F-retinal. This claim scope was not confirmed until the Advisory Actions mailed December 2 and 22, 2010. Therefore, there are good and sufficient reasons why the evidence is necessary and was not earlier presented. To ignore the evidence would be willful ignorance of facts underlying Chapple et al.

Reference 14 cited in Chapple et al. is Saliba et al., "The Cellular Fate of Mutant Rhodopsin: Quality Control, Degradation and Aggresome Formation" J. Cell Sci. (2002) vol. 115, pp. 2907-2918. Saliba et al. was indicated as considered by Ex. Huang on the initialed copy of the Second Information Disclosure Statement mailed by the Office on January 27, 2009. An additional copy of Saliba et al. is attached for the Examiner's convenience.

[1] Reference 14 in Chapple et al. is of record in the instant application (see "Second Information Disclosure Statement" filed September 19, 2008).

Alleged rejections under 35 U.S.C. § 103

The Advisory Actions mailed December 2 and 22, 2010 indicate the maintenance of rejections under 35 U.S.C. § 103(a) based on Chapple et al. and Asato et al., as a pair or in further combination with additional cited documents.

The "final" rejection mailed August 25, 2010 and the Advisory Actions mailed December 2 and 22, 2010 all refer to the following statement on page 13, left column, in Chapple et al.:

> We have also shown that addition of 9-*cis*-retinal to cultures expressing P23H mutant opsin improves the amount of opsin that reaches the plasma membrane, whilst having no effect on K296E mutant opsin[14].

As shown in the above quote, the statement refers to Reference 14 in Chapple et al., which is Saliba et al. as identified above.

The rejections maintained by the Office rely heavily upon this quoted statement. The rejections also contend that in Chapple et al., the statement means that

> "the [9-*cis*-retinal] can be used as a 'chemical' chaperone to stabilize the folding of the mutant opsins shifting the equilibrium toward functional proteins which means Chapple was able to stabilize this particular P23H mutant rhodopsin to be functional/work" (see Advisory Actions mailed December 2 and 22, 2010.

The above contention includes an unsupported assertion of functionality in the "retinoid stabilized" P23H mutant rhodopsin. But neither Chapple et al. nor Asato et al. state that the resulting rhodopsin is a functional rhodopsin analogue. Similarly, Saliba et al. do not disclose any functional rhodopsin analogue. The instant invention is also not based upon the resulting rhodopsin as having functionality as a visual pigment.

In contrast, Saliba et al. provide evidence indicating that movement of P23H mutant opsin to the plasma membrane is insufficient to address deleterious effects of the P23H mutation, such as the formation of aggresomes. Saliba et al. report results from applying 9-*cis*-

retinal in the media of simian (monkey) COS-7 cells modified to express the P23H mutant opsin (see for example, the abstract). With respect to targeting of P23H mutant opsin to the plasma membrane, page 2914 of Saliba et al. states as follows:

> 9-cis-retinal promotes the targeting of P23H mutant opsin to the plasma membrane
>
> Previous studies have suggested that the addition of 11-cis-retinal and 9-cis-retinal to mutant-opsin-expressing cells can improve the folding of mutant opsins (Li et al., 1998a). Therefore, we examined the effect of 9-cis-retinal on mutant opsin processing and aggresome formation in P23H-opsin-expressing cells. The 9-cis-retinal increased the level of mutant opsin as assessed by western blotting and in particular the mature form of the protein in the soluble fraction, suggesting efficient transit through the Golgi apparatus (Fig. 10). This was confirmed by immunocytochemical analysis of opsin localisation (Fig. 10), as an increase in plasma membrane staining with P23H could be observed. However, the incubation of 9-cis-retinal did not lead to a significant decrease in the formation of aggresomes over the period of the treatment time. The addition of 9-cis-retinal to K296E opsin expressing cells had no effect on the processing of the mutant opsin (data not shown), as would be expected as the mutation has removed the site of retinal attachment.

The boxed portion in the above quote clearly indicates that 9-*cis*-retinal "did **not** lead to a significant decrease in the formation of aggresomes" (emphasis added). The retention of aggresomes is important because Saliba et al. also report that "in the presence of mutant protein aggresomes, the normal wild-type protein can be recruited to the inclusions" (see page 2915, left column, first paragraph, last sentence; pages 2910-2911; and Figure 5 on page 2912).

To a person of ordinary skill in the art at the time of the invention, the above facts mean that the statement in Chapple et al. does **not** indicate a means to treat the P23H mutation. Instead, the facts indicate that 9-*cis*-retinal would **not** alter the expected occurrence of P23H mutant opsin aggresomes and the deleterious recruitment of normal opsin to the aggresomes.

This expectation is also contrary to the instant application, where human cells P23H mutant opsin were observed to be rescued with a retinoid and with predominant

localization in a non-aggregated, "diffuse pattern with significantly greater staining at the cell surface similar to … wild-type opsin, which are predominantly at the plasma membrane (see page 25, paragraph [0084] of the instant application).

None of the above is altered by content in Chapple et al. or Asato et al. For example, the rejection is not supported by a reliance on statements in Chapple et al. regarding use of Vitamin A as having limited therapeutic value in a clinical trial against retinitis pigmentosa (RP) and the *possibility* of a "better" clinical outcome *if* the trial was "focused on patients with misfolding mutations…." Given the above facts from Saliba et al., the statements in Chapple et al. are only mere possibilities when considered in the proper factual context.

The Chapple et al. statements provide no reason to expect a change in the lack of decrease in aggresome formation as reported by Saliba et al. Thus there is nothing to lead the person of ordinary skill in the art to expect success by limiting the clinical trial to the P23H mutation with use of 9-*cis*-retinal. Given no reduction in P23H opsin aggresomes and unwanted recruitment of normal opsin to aggresomes as reported by Saliba et al., it is simply unreasonable to expect success in treating patients with the P23H opsin mutation using 9-*cis*-retinal.

As another example, the rejection argues that "further investigation of [Chapple et al.] methods may lead to therapies for the misfolded protein disease and other conditions…." But this is clearly **not** supported by a reasonable expectation of success in light of the data from Saliba et al. Statements by Chapple et al. that "outcomes might have been better" do **not** create a reasonable expectation that outcomes *will* be better.

In an example of the rejection's reliance on Asato et al., the report of different 9-*cis*-retinal analogues having similar binding characteristics to normal, non-P23H (or wild-type) opsin provides no expectation of success in how the analogues bind or do not bind P23H mutant opsin. The functionality of binding normal, non-P23H opsin, as reported by Asato et al., is clearly a different functionality from binding to P23H mutant opsin. Applicants have repeatedly pointed out evidence of this point, which is the example of 11-*cis*-retinal binding to normal, non-

P23H opsin. But the person of ordinary skill in the art knows that a human subject with autosomal dominant disease RP caused by P23H mutant opsin has a supply of endogenous 11-*cis*-retinal available to bind both the P23H mutant opsin and the normal, non-P23H opsin. The fact that the autosomal dominant condition continues to manifest as disease means that the endogenous 11-*cis*-retinal **does not** bind P23H mutant opsin *to remedy the presence of the mutant opsin*.

This is evidence that binding to normal, non-P23H opsin as reported by Asato et al. **fails** to provide any expectation of successful binding to the P23H mutant opsin. This point remains unaddressed by the Office in the rejections and the Advisory Actions to date.

Next, the focus on statements in Chapple et al. regarding 9-*cis*-retinal as a chaperone is insufficient to overcome the facts from Saliba et al. These facts include the observations that promoting localization of P23H mutant opsin to a monkey cell's plasma membrane does not significantly reduce the formation of aggresomes. The Chapple et al. statements also do not negate the phenomenon of the aggresomes recruiting normal, non-P23H opsin.

Finally, Applicants point out that a comparison of Saliba et al. to the instant invention indicates the presence of unexpected factors that support an expectation of success not present in the cited documents. Saliba et al. report the targeting of P23H mutant opsin to a monkey cell's plasma membrane without indication of whether the P23H mutant opsin was properly folded or glycosylated. This is in contrast to the instant invention, which includes evidence that a retinoid rescued P23H opsin in human cells had a glycosylation pattern similar to normal, non-P23H opsin (see page 24, paragraph [0079] of the instant application).

Saliba et al. also report the use of tunicamycin to inhibit glycosylation of the P23H mutant opsin (see pages 2913 to 2914 and Figure 9 on page 2915). The inhibition resulted in no change to the formation of aggresomes, but an accumulation of unglycosylated P23H mutant protein in the endoplasmic reticulum (ER) is reported. Saliba et al. comment that the "data show that the major effect of inhibiting N-linked glycosylation in COS-7 cells is to prevent

the degradation of the mutant protein and lead to its retention in the ER" (see page 2916, left column). But if the glycosylated form is more suited for degradation of the P23H mutant opsin, the person of ordinary skill in the art would not have expected that glycosylation aided by a retinoid (as disclosed in the instant application) would help P23H folding and avoid degradation.

In light of the foregoing, Applicants respectfully submit that there is no basis to conclude that a person of ordinary skill in the art, provided with the two cited documents, would have found it "obvious" to use 9-*cis*-10-F-retinal to bind P23H mutant opsin and prevent its aggregation in a manner that treats the human disease of RP caused by P23H mutant opsin.

This conclusion is not altered by the inclusion of the documents by Grant et al. ("Treatable forms of Retinitis Pigmentosa with systemic neurological disorders") and/or Lang et al. ("Ocular drug delivery conventional ocular formulations") and/or Geroski et al. ("Drug delivery for posterior segment eye disease").

Therefore, the remaining rejections are misplaced and may be properly withdrawn.

Conclusion

In light of the foregoing, Applicants respectfully submit that the claims are allowable and urge early indication to that effect. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at number below.

Respectfully submitted,

/kawai lau/
(Electronic Signature)
Kawai Lau, Ph.D.
Reg. No. 44,461

PATENTIQUE PLLC
PO Box 50368
Bellevue, Washington 98015
Tel: 425-228-0818
Fax: 425-228-8192